REMARKS

35 U.S.C. §103 Rejections

The Office appears to allege on page 8 of the Office Action that Applicants continued discussion about PKC isozyme sensitivity is not relevant because this feature is not an element of the previously pending claims. Applicants believe that the arguments related to isozyme sensitivity are very relevant to the current 35 U.S.C. §103(a) rejections because:

1) the term "PKC" denotes a whole family of isozymes which have very different physiological roles, and hence are involved in different, unrelated disease states;

2) a skilled artisan would not be motivated to inhibit a particular PKC isozyme in order to treat a disease of interest if that particular PKC isozyme is not involved in the disease of interest;

3) a skilled artisan would not have a reasonable expectation of succeeding in treating a disease of interest by inhibiting a particular PKC isozyme if that particular PKC isozyme is not involved in the disease of interest and

4) the skilled person would instead be taught away from treating a disease of interest by inhibiting a particular PKC isoenzyme that is not involved in the disease of interest.

The isozyme-based arguments relate, not to a claim feature, but rather to whether a skilled artisan would select 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione (compound A hereinafter) or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione (compound B hereinafter) from Heath to treat organ or tissue transplant rejection, graft-versus-host disease or to prolong graft survival. Heath warns that that "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state. For example, the elevated blood glucose levels found in diabetes leading to an isozyme-specific elevation of the beta-2 isozyme in vascular tissues." (Heath, Column 1, lines 45-49). Thus, Heath very clearly teaches that the compounds therein are useful in treating disease states associated with an elevation of the beta-1 and beta-2 isozymes. (Heath, Column 2, lines 33-38). Accordingly, if a given disease state is not associated with the PKC beta-1 and beta-2 isozymes, then a skilled artisan would not select a Heath compound to treat that particular disease state. The Office has not established that organ or tissue transplant rejection, graft-versus-host disease or the prolongation of graft survival are associated with the PKC beta-1 and beta-2 isozymes, such that a skilled artisan would select any Heath compound to address these disease states. Moreover, the Office still has yet to provide any rationale why a skilled artisan would select the particular compounds recited in

Applicants' claims to treat organ or tissue transplant rejection, graft-versus-host disease or to prolong graft survival.

Applicants will now address each 35 U.S.C. §103(a) rejection in turn by discussing the teachings of each reference, and what the combination of cited references teaches given the art as a whole at the time of filing.

Claims 5, 15 and 16 are patentable over Heath et al. in view of Bradshaw et al.

The Examiner has rejected claim 5, 15 and 16 under 35 U.S.C. §103(a) as unpatentable over Heath in view of Bradshaw. The Office's argument is that Heath provides the PKC inhibitors identified in Applicants' claims and Bradshaw teaches the therapeutic potential of bis-indolylmaleimides that are selective[1] for PKC, e.g., RO31-845 and RO 31-8830. The Office alleges that Bradshaw teaches that this class of compounds inhibit T-cell proliferation and "because of this function, they would be useful for treating transplant rejection." (Office action at page 4). The Office concludes that because PKC inhibitor bis-indolylmaleimides "as a class" have been recognized as useful in treating transplant rejection, a skilled artisan would have a reasonable expectation of success in treating transplant rejection using Heath compounds "since transplant rejection is a type of inflammation, and Heath et al. teaches that the compounds are useful for treating inflammation." (Office Action at page 5).

For the following reasons, the rejection is respectfully traversed.

What Heath teaches

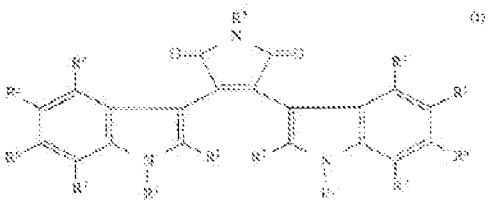
The Office alleges that Heath teaches various PKC inhibitors (including compounds A and B) and their role in various conditions, e.g., inflammation, CNS disorders, etc., but admits that Heath does not teach treatment of transplant rejection.[2]

[1] By "selective", Bradshaw is referring to the selectivity of compounds for PKC over other different enzymes, e.g., serine/threonine kinases, PKA, etc. Bradshaw does not use the term "selective" to refer to compounds selective for particular isozymes of PKC (e.g., PKC beta, PKC alpha, PKC theta, etc.).

[2] The Office notes that Applicants' specification recites Heath as a mode of synthesizing the compounds recited in Applicants' claims. While Applicants selected Compound A and Compound B from the genus of Heath, this is not evidence that another would select Compound A and Compound B from Heath. Applicants' disclosure may not be relied upon in the instant obviousness rejection. Such reliance is pure hindsight and is strictly proscribed by the Office and the courts. Thus, it is irrelevant that Applicants' specification recites Heath as a mode of synthesizing the compounds recited in Applicants' claims.

Heath teaches an extremely large genus of PKC inhibitors. (See Heath, Column 2, lines 47 – column 5, line 23). That genus is as follows:

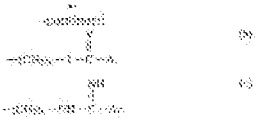
Formula I:



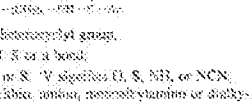
wherein:

R^1 and R^2 are independently hydrogen, alkyl, haloalkyl, alkenyl, arylalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, acylaminoalkyl, acyloxyalkyl, cyanoalkyl, amidinoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, or a group of the formula:

$-(CH_2)_n-W-Het,$



(I)



(Ia)

Het signifies a heterocyclyl group.

W signifies NR^{11} S or a bond.

Y signifies NH or S. V signifies O, S, NR, or NCN.

A signifies alkylthio, amino, monoalkylamino or dialkylamino;

Ar signifies aryl;

R^{1} and R^{2} are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_6 alkylthio, S(O)C_1–C_6 alkyl, CF_3, or R^{1} and R^{2} can combine to form —(CH$_2$)$_3$—X—CH$_2$—;

R^{3} is hydrogen or CH$_3$CO;

R^{4}, R^{5}, R^{6}, R^{7}, R^{8}, R^{9}, R^{10} and R^{11} are independently hydrogen, halogen, alkyl, hydroxy, alkoxy, —COOC$_1$–C$_6$ alkyl, CF$_3$, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_6 alkylthio, or S(O)C_1–C_6 alkyl;

X is CHR^{6} or NR^{6},

R^{6} is (CH$_2$)$_q$R^{12},

R^{12} is hydrogen, hydroxy, alkoxy, amino, monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl,

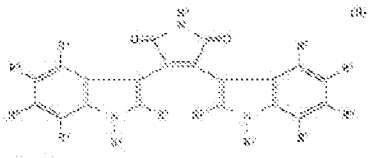
n is 1, 2, 3, 4, 5 or 6,

r is 1, 2, or 3; and

s is 0, 1, 2 or 3

As selective inhibitors, the invention further provides a method for treating diseases mediated, which comprises administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound of the Formula I.

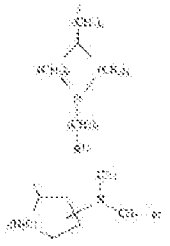
In addition, the present invention provides novel compounds which are isozyme selective PKC inhibitors, of the Formulas II, III, and IV:



(II)

wherein:

R^{1} is



(IIa)

R^{2} is

(IIb)

R^{3} is hydrogen, C_1–C_6 alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R^{4} and R^{5} are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_6 alkylthio, S(O)C_1–C_6 alkyl, CF_3;

R^{6} is hydrogen or CH$_3$CO—;

R^{7}, R^{8}, R^{9}, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently hydrogen, halogen, alkyl, hydroxy, alkoxy, —COOC$_1$–C$_6$ alkyl), CF$_3$, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_6 alkylthio, or S(O)C_1–C_6 alkyl;

R^{15} is hydrogen, alkyl, haloalkyl, cycloalkyl, acetyl, aryl, —CH(aryl)$_2$, amino, monoalkylamino, dialkylamino, guanidino, —C(=NH)—N (alkoxycarbonyl)$_2$, N(alkoxycarbonyl), amidino, hydroxy, carboxy, alkoxycarbonyl or heterocyclyl;

p and q are independently 1, 2, 3, or 4;

r is 0, 1, 2 or 3,

s is 1 or 2,

u is 0 or 1; or

pharmaceutically acceptable salts or solvates thereof.

(III)

wherein:

R^{1} is hydrogen, C_1–C_6 alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R^{2} is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_6 alkylthio, S(O)C_1–C_6 alkyl, CF_3;

R^{3} is hydrogen or CH$_3$CO—;

R^{4}, R^{5}, R^{6}, R^{7}, R^{8}, R^{9}, R^{10} and R^{11} are independently hydrogen, halogen, alkyl, hydroxy, alkoxy, —COOC$_1$–C$_6$ alkyl), CF$_3$, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_6 alkylthio, or S(O)C_1–C_6 alkyl;

X is C(R^{6})$_2$;

R^{6} is (CH$_2$)$_q$R^{12};

R^{12} is (CH$_2$)$_q$R^{13};

R^{13} and R^{14} are independently hydroxy, alkoxy, carboxy, acyloxy, amino, monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl;

r is 1, 2, or 3;

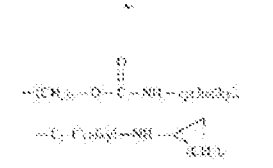
s is 0, 1, 2 or 3; or

pharmaceutically acceptable salts or solvates thereof.

(IV)

wherein:

R^{1} is



or alkylglycose residue;

R^{2} is hydrogen, C_1–C_6 alkyl, cyclopropylmethyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R^{3} and R^{4} are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_6 alkylthio, S(O) C_1–C_6 alkyl, CF_3;

R^{5} is hydrogen or CH$_3$CO—;

R^{6}, R^{7}, R^{8}, R^{9}, R^{10}, R^{11}, R^{12} and R^{13} are independently hydrogen, halogen, alkyl, hydroxy, alkoxy, —COO (C_1–C_6 alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_6 alkylthio, or S(O)C_1–C_6 alkyl;

n is 1, 2, 3, 4, 5 or 6; or

pharmaceutically acceptable salts or solvates thereof.

In addition to this extremely large genus, Heath teaches that the compounds therein are highly selective inhibitors of the PKC beta 1 and PKC beta 2 isozymes (see, e.g., Heath, Column 2, lines 28-34). Heath warns that that "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state. For example, the elevated blood glucose levels found in diabetes leading to an isozyme-specific elevation of the beta-2 isozyme in vascular tissues," effectively ensuring that a skilled artisan would very carefully select a PKC inhibitor that would target the PKC isozyme involved in a disorder of interest (Heath, Column 1, lines 45-49).

Heath indicates that, because of the isozyme selectivity of the disclosed compounds, such compounds are useful in treating disease states associated with an elevation of the beta-1 and beta-2 isozymes. (Heath, Column 2, lines 33-38). Heath teaches that the highly selective inhibitors of the PKC beta 1 and PKC beta 2 isozymes therein may be used to treat conditions associated with diabetes mellitus and its complications "as well as other disease states associated with an elevation of the beta-1 and beta-2 enzyme." (Heath, Abstract). At columns 11 and 12, Heath asserts that the compounds therein may be used to additionally treat ischemia, inflammation, CNS disorders, cardiovascular disease, dermatological disease, Alzheimer's disease and cancer.

Compounds A and B are shown in Examples 49 and 52 of Heath, wherein these compounds have IC_{50}'s for PKC beta-1 and beta-2 isozymes of 0.03 μM. The compound of Example 49 has an IC_{50} for PKC alpha of 0.8 μM, which is about 30 times less sensitive than the effect of said compound on PKC beta isozymes, and the compound of Example 52 has an IC_{50} of 0.3 μM, which is 10 times less sensitive than the effect of said compound on PKC beta isozymes. A skilled artisan, viewing Heath would understand that Compound A and Compound B selectively inhibit PKC beta, especially in light of the strong and clear statements in Heath that his compounds are "selective protein kinase C beta-1 and beta-2 isozyme inhibitors." (Heath, Abstract).

What Bradshaw teaches

Bradshaw teaches bis-indolylmaleimides that are selective for PKC over other protein kinases and which may provide "more appropriate tools to investigate the role of PKC in cellular processes." (Bradshaw, Abstract). Bradshaw discusses the various possible roles of PKC inhibitors, suggesting a wide range of conditions which they might be useful against e.g. rheumatoid arthritis, lupus, diabetes, asthma, multiple sclerosis, Alzheimer's disease, malignantly glioma, hypertension, cystic fibrosis, to mention but a few. Transplant rejection appears among this broad-

ranging and very speculative list, and the document fails to give any data or evidence to support these speculations. The authors believe that PKC inhibitors inhibit T-cell proliferation, and that compounds which inhibit T-cell proliferation (as shown by cyclosporin A) "may have a role to play" in the area of transplant rejection. (Bradshaw p. 138). The Office's allegation of obviousness in view of Bradshaw is based on the skilled person having to make a series of deductions, none of which are directly or logically connected. The portion of Bradshaw that discusses evidence for PKC involvement in transplant rejection states that lymphocyte-mediated myocyte injury was prevented if the lymphocytes were pre-treated with phorbol esters to deplete PKC before introduced into an *in vitro* model of cellular damage. (Bradshaw, p138).

On page 141, Bradshaw states (emphasis added):

> [f]rom the forgoing discussion it would seem likely that a very wide range of potential therapeutic applications exist for PKC inhibitors; *however much of the evidence which has been used to implicate PKC contains serious flaws.* The ability to stimulate a physiological process with direct activators of PKC such as phorbol esters *does not preclude alternative pathways which might be used by physiological agonists.*

On page 142, Bradshaw states (emphasis added):

> Ro 31-8830 *is inactive in a whole range of models of acute inflammation* suggesting a selective action which could not be readily predicted from in vitro and in vivo studies with K252a and staurosporine.

What Heath and Bradshaw Teach in View of the Art as a Whole

Given the above teachings, a skilled artisan would not select any PKC beta 1 or 2 inhibitor from Heath for the treatment of organ or tissue transplant rejection or for the prolongation of graft survival, let alone compound A and B as recited in the currently-pending claims.

The disclosure of Bradshaw merely teaches that one should use bis-indolylmaleimides to *study* the role of PKC in cellular processes. This is because Bradshaw teaches that earlier studies using non-selective PKC inhibitors (e.g., phorbol esters), which include the studies relied on by the Office (i.e., the transplant studies referred to by Bradshaw on p. 138 as supporting a role for PKC in transplant rejection) were *flawed* and do not preclude alternative pathways being involved in a

particular disease state. (Bradshaw at p. 141). In addition, Bradshaw teaches that the bis-indolylmaleimides (e.g, Ro 31-8830, a compound cited by the Office as being within the formula of Heath) can be inactive in a whole range of models of acute inflammation (Bradshaw at p. 142). Thus, Bradshaw admits the speculative nature of earlier PKC studies, including transplant studies, and provides evidence that there is a high level of unpredictability in using bis-indolylmaleimide PKC inhibitors.

Furthermore, Bradshaw was published in 1993, i.e. 11 years before the priority date of the present application. At that time little was known about the role of PKC and in particular the role of its various isoforms. While the age of a reference may not be used to disqualify a reference as part of an obviousness rejection, it is certainly more relevant to consider what was known in the art at the time of filing (rather than what was known over a decade before the filing date). By the time of filing the instant application, various isoforms of PKC had been more clearly distinguished and were understood to have different physiological roles – see Baier et al. (2003) Immunological Reviews 192:64-79. This document reflects more accurately the state of the art near the time of filing of the present application. Baier sets out that the PKC theta isoform is a central regulator of T cell proliferation (see, for example page 74, right column) and hence the skilled person at the time of filing would expect PKC theta to play a key role in transplant rejection. The PKC alpha isoform is also described as essential in T cell biology (see, for example p76, left column). The skilled person wanting to develop a drug for treating transplant rejection (or GvHD as in claims 17-19) would therefore focus on compounds having potent and selective activity towards PKC alpha and theta.

Heath clearly describes its compounds as being specifically selective inhibitors against PKC beta-1 and beta-2 isoforms (see Heath Abstract). Moreover, compound A, which appears as Example 49 in Heath, clearly demonstrates the selectivity towards the beta isoforms. Activity against PKC alpha on the other hand is rather low, at 800 nM, while PKC theta activity is not even measured. The skilled person, having read, e.g., Baier et al, and realizing the PKC alpha and theta isoforms are relevant for transplant rejection, would not consider any of the compounds within Heath to be useful for these indications. In fact, Heath warns that only certain PKC isozymes are associated with certain disorders and the broad list of disorders in Bradshaw is not correlated with any specific PKC isozymes. Thus, a skilled person would try to identify compounds selective against only the alpha and theta isoforms rather than the beta or any other isoforms. Accordingly, there is no apparent reason that one of skill in the art would select compound A or compound B (which are selective PKC beta inhibitors) from Heath for use in Applicants' methods.

A reasonable expectation of success remains a main element of any proper *prima facie* case of obviousness. However, as discussed above, Bradshaw provides evidence that there is a high level of unpredictability in using PKC inhibitors – even among bis-indolylmaleimides. This, coupled with the warnings of Heath regarding isozyme specificity, and the teachings of Baier et al. regarding the role of PKC alpha or theta in regulating T cell proliferation, establishes that there is no expectation of success in using a PKC beta inhibitor to treat transplant rejection or promote graft survival.

Teaching away from a particular invention is *prima facie* evidence of the non-obviousness of the invention. The art as a whole teaches away from Applicants' claimed subject matter. Heath emphasizes that only one or two PKC isozymes may be involved in a given disease state (and Heath does not link transplant rejection to PKC beta). Baier et al. teaches that PKC alpha and theta are involved in the regulation of T cell proliferation, which has a central role in transplant rejection. Thus, Heath and Baier establish that one should NOT use the selective PKC beta inhibitors of Heath to treat transplant rejection or promote graft survival.

There are additional reasons that the pending claims are patentable over the cited art. One would not be motivated to use compound A and B from Heath to treat transplant rejection for the following reasons:

1) the genus of compounds in Heath is very large and there is no motivation to select the two specific compounds recited in Applicants' claims; and
2) the genus of disorders in Bradshaw is very large and there is no motivation to select the specific disorders recited in Applicants' claims;

As identified in point #1 and #2, above, for the instant claims there are at least two genera from the cited art that one must address for an obviousness determination: 1) the compounds used; and 2) the disorders treated. Moreover, for a proper obviousness analysis, one must consider what the cited art as a whole explicitly states or inherently implies about these genera.

While the Supreme Court in KSR v. Teleflex, 127 S.Ct. 1727 (2007) has rejected the rigidity of the "teaching, suggestion or motivation test" and allows motivation to be found via other avenues – the Office must provide some reason to select portions from a cited reference. Indeed, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441

F.3d 977, 988 (Fed. Cir. 2006). The Office has yet to identify the rational underpinning to select compound A and compound B from the very large genus of Heath, to select prevention or treatment of transplant rejection from Bradshaw, and to combine these selections together. Without such rationale, no obviousness rejection can be maintained.

The Office alleges that because PKC inhibitor bis-indolylmaleimides "as a class" have been recognized as useful in treating transplant rejection, a skilled artisan would have a reasonable expectation of success in treating transplant rejection using Heath compounds "since transplant rejection is a type of inflammation, and Heath et al. teaches that the compounds are useful for treating inflammation." (Office Action at page 5). This is legally and scientifically incorrect. It does not follow that a compound is useful to treat transplant rejection, prolong graft survival, or treat GVHD simply because the compound treats inflammation. Aspirin, ibuprophen, acetaminophen, etc., ALL reduce inflammation, and none are indicated for transplant rejection. Thus, that a Heath compound can be used to treat inflammation does not mean that a Heath compound will be useful to treat transplant rejection, prolong graft survival, or prevent GVHD.

For at least these reasons, please withdraw the outstanding obviousness-based rejection of claims 5, 15 and 16.

Claims 5, 15, 16 and 20-22 are patentable over Heath et al. in view of Albert et al.

The Examiner has rejected claim 5, 15, 16 and 20-22 under 35 U.S.C. §103(a) as unpatentable over Heath in view of Albert. The Office's argument is that Heath provides the PKC beta inhibitors identified in Applicants' claims, that Albert teaches bis-indolemaleimide compounds that overlap in scope with the compounds of Heath, and that Albert teaches the use of these compounds to treat "T-cell mediate acute or chronic inflammatory disease or disorders, autoimmune diseases, graft rejection (transplant rejection)." (Office Action at page 5). The Office concludes that it would be obvious to use the bis-indolemaleimide compounds of Heath in a method for prolonging graft survival and/or treating transplant rejection, since PKC inhibitor bis-indolemaleimide have been recognized by Albert for doing so, and because compounds "having similar structure an function [are] useful for the same purposes" (Office Action at p. 6).

This Office's argument, in general, is one of equivalency, which is outlined in MPEP 2144.06, which states:

> In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents.

Therefore, for the Office's argument to be proper, the Office must establish that the PKC beta inhibiting compounds of Heath were known prior to Applicants' filing date to be equivalent to the compounds of Albert, such that one might select a Heath compound for use in an Albert method.

For the following reasons, this rejection is respectfully traversed.

What Heath teaches

The teachings of Heath are described above

What Albert teaches

Albert discloses a large genus of PKC inhibitors and their use to treat a very large genus of disorders. For example, Albert claims that the PKC inhibitors therein are

> useful in the treatment and/or prevention of diseases or disorders mediated by T lymphocytes and/or PKC, e.g. acute or chronic rejection of organ or tissue allo- or xenografts, atherosclerosis, vascular occlusion due to vacular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS diseases such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious diseases such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock. The compounds of formula I are also useful in the treatment and/or prevention of T-cell mediated acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, respiratory diseases such as asthma or inflammatory lung injury, inflammatory liver injury, inflammatory

glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis), inflammatory eye diseases, e.g. Sjoegren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

Albert shows data at [0237]-[0244] that suggests that the compound of Example 56 (sotrastaurin, a PKC theta inhibitor according to [0226]) and Example 100 (a PKC alpha inhibitor according to [0228]) may be useful for promoting graft survival and in transplant indications. The Office has previously insisted that the compounds of Albert are also PKC beta inhibitors (See Office Action date September 23, 2009 at page 4). While a large enough dose of any compound could theoretically inhibit PKC beta, the ONLY compounds exemplified by Albert to address transplantation are a PKC alpha inhibitor (compound 100) and a PKC theta inhibitor (compound 56). No such testing is provided for any PKC beta inhibitor of Albert (even though Albert clearly discloses PKC beta inhibitors in the Examples). Therefore, Albert teaches that a particular PKC alpha and a particular PKC theta inhibiting compound may be useful in addressing transplant rejection. As for the other compounds and disorders of Albert, Albert does not indicate which PKC isozymes are associated with which disorders. Applicants note that this teaching of Albert of great concern according to Heath because "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state".

Albert does not disclose any bisindolylmaleimide compounds (see structural definition of the compounds encompassed – R is not an indole group). Hence there is no overlap in scope between the compounds of Albert and Heath. The Office's assertion that "since PKC inhibitor bisindolylmaleimides have been recognized in the prior art [for prolonging graft survival and or treating transplant rejection] as taught by Albert" is therefore incorrect.

What Heath and Albert Teach in View of the Art as a Whole

Based on the above teachings, a skilled artisan would not select any PKC beta 1 or 2 inhibitor from Heath for the treatment of organ or tissue transplant rejection or for the prolongation of graft survival, let alone compound A and B as recited in the currently-pending claims.

Given the notable structural differences between the compounds of Heath and Albert, the skilled person would not consider the compounds to be equivalent, nor would the skilled person try to combine Heath and Albert. As already noted above, Heath clearly describes compounds which are selective inhibitors of the beta-1 and beta-2 isoforms of PKC. In contrast, Albert describes compounds which are structurally different, and which are not specifically targeted towards inhibition of the beta isoforms. It would be readily recognized by any skilled person in the art that small structural changes to a molecule will result in vast differences in activity, let alone selectivity against different biological targets. The compounds of Heath and Albert differ structurally in several aspects, and therefore the activity of the Albert compounds cannot be extrapolated to form any expectation as to the activity of the heath compounds.

Heath also warns that only certain PKC isozymes are associated with different disorders. However, the large list of disorders in Albert is not correlated with specific PKC isozymes. In Albert, only a PKC alpha or theta inhibitor is used to address transplant rejection. In Heath there is an extremely broad genus of selective inhibitors of PKC beta 1 and beta 2. Accordingly, there is no apparent reason that one of skill in the art would select compound A or compound B for use in Applicants' methods. There is simply no evidence that the selective PKC beta-inhibiting compounds of Heath are equivalent to the PKC alpha and theta inhibitors of Albert, such that substitution of one for the other would be routine and obvious.

A reasonable expectation of success remains a main element of any proper *prima facie* case of obviousness. However, the warnings of Heath regarding isozyme specificity, and the teachings of Baier et al. regarding the role of PKC alpha or theta in regulating T cell proliferation, establishes that there is no expectation of success in using a PKC beta inhibitor to treat transplant rejection or promote graft survival.

Teaching away from a particular invention is prima facie evidence of the non-obviousness of the invention. The art as a whole teaches away from Applicants' claimed subject matter. Heath emphasizes that only one or two PKC isozymes may be involved in a given disease state (and Heath does not link transplant rejection to PKC beta). Baier et al. teaches that PKC alpha and theta are involved in the regulation of T cell proliferation, which has a central role in transplant rejection. Thus, Heath and Baier establish that one should NOT use the selective PKC beta inhibitors of Heath to treat transplant rejection or promote graft survival.

There are additional reasons that the pending claims are patentable over the cited art. One would not be motivated to use a Heath compound to treat transplant rejection or prolong graft survival for the following reasons:

3) the genus of compounds in Heath is very large and there is no motivation to select the two specific compounds recited in Applicants claims; and
4) the genus of disorders in Albert is very large and there is no motivation to select the specific disorders recited in Applicants claims;

As identified in point #1 and #2, above, for the instant claims there are at least two genera from the cited art that one must address for an obviousness determination: 1) the compounds used; and 2) the disorders treated. Moreover, for a proper obviousness analysis, one must consider what the cited art as a whole explicitly states or inherently implies about these genera.

While the Supreme Court in KSR v. Teleflex, 127 S.Ct. 1727 (2007) has rejected the rigidity of the "teaching, suggestion or motivation test" and allows motivation to be found via other avenues – the Office must provide some reason to select portions from a cited reference. Indeed, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The Office has yet to identify the rational underpinning to select compound A and compound B from the very large genus of Heath, to select prevention or treatment of transplant rejection or prolongation of graft survival from Albert, and to combine these selections together. Without such rationale, no obviousness rejection can be maintained.

For at least these reasons, please withdraw the outstanding obviousness rejection of Claims 5, 15, 16 and 20-22.

Claims 17-19 are patentable over Heath et al. in view of Albert et al., further in view of Goekjian.

The Office has rejected claim 17-19 under 35 U.S.C. §103(a) as unpatentable over Heath in view of Albert, further in views of Goekjian et al. (all of record). The Office's argument is that Heath provides the two indolymaleimide derivative PKC beta inhibitors identified in Applicants' claims and Albert teaches that certain other indolymaleimide derivatives that inhibit PKC can be used to treat "T-cell mediate acute or chronic inflammatory disease or disorders, autoimmune disease, graft rejection or cancer." (Office Action dated July 1, 2009 at pages 3-4). The Office admits that graft vs

host disease (GVHD) is not disclosed in either Heath or Albert, and thus turns to Goekjian, which is alleged to teach that a PKC beta inhibitor can be used to treat GVHD. (Office Action at page 8). The Office alleges that there is very close structural and functional similarities of the compounds of Heath et al. and RO32-0432 (Office Action at page 7).

The Office's argument, in general, is one of equivalency, which is outlined in MPEP 2144.06, which states:

> In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents.

Therefore, for the Office's argument to be proper, the Office must establish that the PKC beta inhibiting compounds of Heath were known prior to Applicants' filing date to be equivalent to the compounds of Goekjian, such that one might select a Heath compound for use in a Goekjian method of treating GVHD.[3]

For the following reasons, the rejection is respectfully traversed.

What Heath teaches

The teachings of Heath are described above.

What Albert teaches

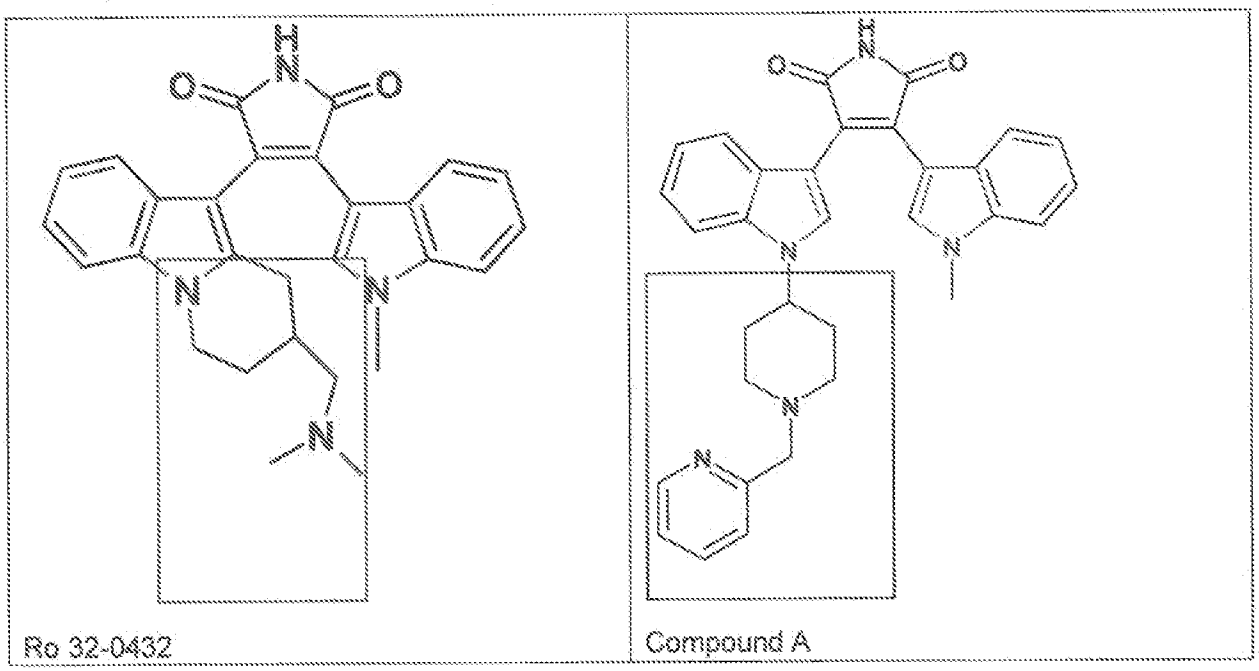
The teachings of Albert are described above.

Applicants reemphasize that Albert does not disclose any bisindolylmaleimide compounds (see structural definition of the compounds encompassed – R is not an indole group). Hence there is no overlap in scope between the compounds of Albert and Heath.

What Goekjian teaches

[3] Applicants note that on page 6 of the Office Action, the Office alleges that the compounds of Albert "strongly resemble" RO32-0432 as disclosed in Goekjian. First, this is not correct – as Albert does not disclose any bisindolylmaleimide compound (and Ro 32-0432 is a bisindolylmaleimide). Second, this is not relevant - as the showing that must be made is that one would select compound A and B from HEATH (not Albert, which does not disclose compound A or B) for use in a Goekjian method.

Goekjian, as indicated by title, is focused on cancer uses of PKC inhibitors. GVHD is mentioned in Goekjian, but the PKC inhibitor used to treat inflammation and GVHD in rats in Goekjian, i.e., RO32-0432, is structurally very different from compounds A and B of the present invention and is conformationally restricted (i.e., the position of the amine substituent with respect to the rest of the molecule), as noted on page 2131, left column. Below is the structure of RO32-0432 in comparison to the structure of compound A:



As is evident, the difference in chemical structure between Ro 32-0432 and compound A is dramatic (see boxed areas).

Table 4 in Goekjian teaches that RO32-0432 is a PKC alpha inhibitor, having an IC_{50} of 9 nM for PKC alpha and an IC_{50} of between 28-31 nM for PKC beta 1 and 2 isozymes. Table 4 of Goekjian also analyzes a very selective and strong PKC beta inhibitor – i.e., LY-333531, having an IC_{50} of between 5-6 nM for PKC beta 1 and 2 isozymes (and only 360 nM for PKC alpha). Goekjian discusses the excellent selectivity of LY-333531 for PKC beta isozymes on page 2131. Goekjian teaches that LY-333531 is useful in treating diabetic retinopathy and cancer on page 2132.

What the combination of Goekjian, Albert and Heath Teach in View of the Art as a Whole

Given the above teachings, a skilled artisan would not select any PKC beta 1 or 2 inhibitor from Heath for the prophylaxis of graft-versus-host disease, let alone compound A and B as recited in the currently-pending claims.

It is well known that small differences in chemical structure can result in vast variations in biological activity and selectivity. A skilled person having knowledge of the large structural differences between Ro 32-0432 and compound A (and compound B) would not therefore be led to make any assumptions or predictions as to the activity of compound A.

Heath warns that only certain PKC isozymes are associated with different disorders and provides an extremely broad genus of selective inhibitors of PKC beta 1 and beta 2. Goekjian teaches that RO32-0432, the only compound mentioned in Goekjian to show use in GVHD, is a PKC alpha inhibitor (see also, Birchall et al (1994) J. Pharmacology and Exp. Therapeutics 268:922 at p. 926 Table 2, showing the PKC alpha isozyme selectivity of RO32-0432). Goekjian reinforces the teachings from Baier et al., i.e., selectivity against PKC alpha or PKC theta - and not PKC beta - is necessary to address transplant concerns. Accordingly, there is no apparent reason that one of skill in the art would select compound A or compound B from Heath for use in GVHD as taught by Goekjian. There is simply no evidence that the selective PKC beta-inhibiting compounds of Heath are equivalent to the PKC alpha inhibitors of Goekjian, such that substitution of one for the other would be routine and obvious.

If, as the Office alleges on page 7 of the Office Action, RO32-0432 is actually a selective PKC beta inhibitor – why would the Goekjian authors not emphasize this as they did for LY-333531? The question for an obviousness analysis is what does the art *as a whole* teach or suggest? *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (stating that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention).[4] A skilled artisan, viewing Goekjian would understand that RO32-0432 selectively inhibits PKC alpha and that it can be used to treat GVHD, while LY-333531 selectively inhibits PKC beta and that it can be used to treat cancer or retinopathy. Accordingly, there is no apparent reason that one of skill in the art

[4] The MPEP specifically requires the Office to "consider[] both the invention and the prior art references as a whole" and warns of distilling an invention down to a "gist" or "thrust", as such distillation disregards the "as a whole" requirement for an obviousness analysis. *See W.L. Gore*, 721 F.2d 1540 (Fed. Cir. 1983); MPEP § 2141.02.

would select an inhibitor of PKC beta for use in preventing GVHD, especially when a skilled artisan has been taught by Baier et al. and Heath to carefully choose a PKC inhibitor that matches the PKC isozyme target.

A reasonable expectation of success remains a main element of any proper *prima facie* case of obviousness. However, as discussed above, Bradshaw provides evidence that there is a high level of unpredictability in using PKC inhibitors – even among bis-indolylmaleimides. This, coupled with the warnings of Heath regarding isozyme specificity, and the teachings of Baier et al. regarding the role of PKC alpha or theta in regulating T cell proliferation, establishes that there is no expectation of success in using a PKC beta inhibitor to prevent GVHD.

Teaching away from a particular invention is prima facie evidence of the non-obviousness of the invention. The art as a whole teaches away from Applicants' claimed subject matter. Heath emphasizes that only one or two PKC isozymes may be involved in a given disease state (and Heath does not link transplant rejection to PKC beta). Baier et al. teaches that PKC alpha and theta are involved in the regulation of T cell proliferation, which has a central role in transplant rejection. Thus, Heath and Baier establish that one should NOT use the selective PKC beta inhibitors of Heath to prevent GVHD.

Finally, the genus of compounds in Heath is very large and there is no motivation to select the two specific compounds recited in Applicants' claims. For a proper obviousness analysis, one must consider what the cited art as a whole explicitly states or inherently implies about this genus. While the Supreme Court in KSR v. Teleflex, 127 S.Ct. 1727 (2007) has rejected the rigidity of the "teaching, suggestion or motivation test" and allows motivation to be found via other avenues – the Office must provide some reason to select portions from a cited reference. Indeed, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The Office has yet to identify the rational underpinning to select compound A and compound B from the very large genus of Heath. Without such rationale, no obviousness rejection can be maintained

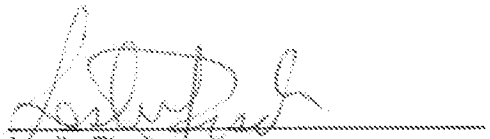
For at least these reasons, Applicants respectfully submit that claims 17-19 are not obvious. Please withdraw the outstanding obviousness-based rejection of claims 17-19.

CONCLUSION

In view of the foregoing distinctions and remarks, Applicants submit that the presently claimed invention is neither disclosed nor suggested by the cited references, and that all the criteria of 35 U.S.C. §112 are satisfied for the instant application. Accordingly, favorable reconsideration of the application is earnestly solicited.

Please send any further correspondence relating to this application to the undersigned attorney at the address below.

Respectfully submitted,



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